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(54) Title of the Invention: **Composition for Readily Absorbable Solid Preparation of AS-56C**

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SPECIFICATION

1. Title of the Invention

Composition for Readily Absorbable Solid Preparation of AS-56C

2. Claims

(1) A composition for a solid preparation of AS-56C, characterized in that 4-(cis-p-methan-8-yloxy)benzanilide (AS-56C) is present in a substantially amorphous state in one or more bases selected from the group consisting of hydroxypropyl methyl cellulose phthalate, hydroxypropyl methyl cellulose acetate succinate, methyl acrylate-methacrylic acid-methacrylate copolymers, and methacrylic acid-methyl methacrylate copolymers.

3. Detailed Description of the Invention

The present invention relates to a composition for a readily absorbable solid preparation for 4-(cis-p-methan-8-yloxy)benzanilide (AS-56C), and in particular to a composition for a readily absorbable solid preparation of AS-56C, characterized in that AS-56C is present in a substantially amorphous state in one or more bases selected from the group consisting of hydroxypropyl methyl cellulose phthalate (such as HP-55, trade name by Shin-Etsu Kagaku), hydroxypropyl methyl cellulose acetate succinate (such as HPMC-AS, trade name by Shin-Etsu Kagaku), methyl acrylate-methacrylic acid-methacrylate copolymers (such as MPM-06, trade name by Tanabe Seiyaku), and methacrylic acid-methyl methacrylate copolymers (such as Eudragit L, trade name by Rohm and Haas).

The aforementioned AS-56C is extremely promising as an antilipemic drug which can be orally administered in the form of a compound synthesized for the first time by researchers of Applicant's company. The practical use of this compound, however, has been complicated by it poor water-solubility, poor enteral absorption when taken orally, and poor bioavailability. The inventors undertook extensive pharmaceutical research in the interests of improving the bioavailability of AS-56C, and discovered that the compound can form stable solid solutions with certain bases, resulting in considerably improved enteric absorption when orally administered.

Polyvinyl pyrrolidone (PVP) and the like have generally been used in the past to make poorly water-soluble medicinal products and the like into solid solutions, but the use of PVP does not allow AS-56C to be made into a solid solution, and has afforded virtually no improvement in bioavailability. Subsequent research revealed that the aforementioned bases form favorable solid solutions.

The composition of the present invention is produced in the following manner. That is, the AS-56C and one or a mixture of two or more of the aforementioned bases are dissolved in an organic solvent, and the solvent is then removed. The solvent can be removed by spray drying, heating at ordinary or reduced pressure, or the like. The proportion in which the AS-56C and base are blended will depend on the type of base, but the base can generally be used in an amount of at least 1 part, and preferably at least 2 parts, per part AS-56C. It is also effective to add a small amount of a surfactant to the blend in order to obtain a more favorable composition.

Examples of surfactants which may be used for that purpose include sucrose fatty acid esters and Polysorbate 80.

Organic solvents used to prepare the composition of the present invention are not particularly limited, provided that they can dissolve both the AS-56C and the base. The amount that is used must be an amount sufficient to dissolve these components. Volatile solvents are preferred since they are easier to remove. Methylene chloride, methyl alcohol, isopropyl alcohol, acetone, chloroform, ethyl alcohol, and the like may ordinarily be used, either alone or in suitable combinations.

The composition of the present invention may also be prepared with the addition of colorants, flavors, fragrances, thickeners, and the like as needed.

The composition in the present invention can be prepared in the usual manner as formulations suitable for oral administration, such as powders, granules, tablets, and pills.

Animal experiments and their results are given below to demonstrate the effects of the composition in the present invention.

Animal Experiments (Bioavailability in Dogs)

Experiment 1

Four beagles were divided into three groups comprising one, one, and two animals each. The compositions obtained in Examples 1 and 7, and AS-56C stock powder as a control, were orally administered in a dosage of 25 mg/kg in terms of the AS-56C. Administration was by cross over in one week intervals. The concentration of AS-56C in plasma was determined 1, 2, 4, 6, 8, 10, and 24 hours following administration.

The concentration of AS-56C in plasma was determined in the following manner by mass fragmentography.

0.5 mL (400 mg) benzene solution of deuterium-labeled AS-56C (d_5-AS-56C) was added as an internal reference to 1 mL plasma, 2 mL of 0.5 N sodium hydroxide and 4 mL of benzene were then added, and the mixture was shaken for 15 minutes. The mixture was then centrifuged for 10 minutes, and the organic layer was separated. The organic layer was distilled off *in vacuo*, the residue was dissolved in 50 μL ethyl acetate, and 2 to 3 μL was injected into a gas chromatograph-mass spectrometer. The base line peaks at m/z 213 and m/z 218 for AS-56C and d_5-AS-56C, respectively, were used for ion detection. The results are given in Table 1.

The concentrations of AS-56C in plasma resulting from the administration of the compositions prepared in Examples 1 and 7 were higher, as was the bioavailability, than when the stock powder alone was given. The AUC for the concentration in plasma during the administration of the stock powder was 1.00, whereas it was 16.2 and 21.5 for Examples 1 and 7, respectively.

Table 1

Sample	No. of animals	Concentration of AS-56C in plasma (ng/mL)							AUC plasma conc. (ng/mL-hr)
		1 hr	2 hr	4 hr	6 hr	8 hr	10 hr	24 hr	
Control (powder)	4	24 ±15	30 ±12	23 ±10	14 ±8	5 ±3	3 ±2	0 ±0	157 ±55
Composition Example 1	4	282 ±30	364 ±52	387 ±70	156 ±27	71 ±9	45 ±1	18 ±18	2,540 ±88
Composition Example 7	4	296 ±63	398 ±22	435 ±47	297 ±117	120 ±41	80 ±25	20 ±2	3,368 ±587

Note: Levels in table are mean ± standard deviation

Experiment 2

Six dogs were divided into two groups of three animals each, which were orally administered the compositions obtained in Example 1 or Example 3, respectively, in a dosage of 25 mg/kg in terms of AS-56C. Administration was by cross over in one week intervals. The concentration of AS-56C in plasma was determined 1, 2, 4, 6, 8, and 10 hours following administration in the same manner as in Example 1 to compare the bioavailability of the two groups. The results are given in Table 2. No statistically significant differences were found between the two compositions, in terms of either the plasma concentration over time or the AUC for plasma concentration, indicating that the composition of Example 3 was characterized by the same dramatically improved bioavailability as Example 1 compared to AS-56C stock powder.

Table 2

Sample	No. of animals	Concentration of AS-56C in plasma (ng/mL)						AUC plasma conc. (ng/mL-hr)
		1 hr	2 hr	4 hr	6 hr	8 hr	10 hr	
Control (Composition Example 1)	6	287 ±42	351 ±49	491 ±59	419 ±757	174 ±46	93 ±24	3,074 ±249
Composition Example 3	6	198 ±13	375 ±50	397 ±67	264 ±73	107 ±28	69 ±20	2,365 ±352

Note: Levels in table are mean ± standard deviation

Examples are given below to illustrate methods for producing the compositions of the present invention, and their properties.

Example 1

4 g of AS-56C and 16 g of hydroxypropyl methyl cellulose phthalate were dissolved in a 240 g mixture of methylene chloride and methyl alcohol (95:5). The solution was spray dried.

Example 2

4 g of AS-56C and 12 g of hydroxypropyl methyl cellulose phthalate were dissolved in a 180 g mixture of methylene chloride and methyl alcohol (95:5). The solution was spray dried.

Example 3

8 g of AS-56C and 16 g of hydroxypropyl methyl cellulose phthalate were dissolved in a 160 g mixture of methylene chloride and methyl alcohol (1:1). The solution was spray dried.

Example 4

8 g of AS-56C and 8 g of hydroxypropyl methyl cellulose phthalate were dissolved in a 120 g mixture of methylene chloride and methyl alcohol (95:5). The solution was spray dried.

Example 5

4 g of AS-56C and 16 g of hydroxypropyl methyl cellulose acetate succinate were dissolved in a 160 g mixture of methylene chloride and methanol (1:1).

The solution was placed in Petri dishes, the solvent was evaporated off over an evaporative bath, and the product was dried for 24 hours in a vacuum dryer and milled into a powder in a mill.

Example 6

8 g of AS-56C and 160 g of hydroxypropyl methyl cellulose acetate succinate were dissolved in a 160 g mixture of methylene chloride and methanol (1:1).

The solution was made into a powder in the same manner as in Example 5.

Example 7

4 g of AS-56C and 16 g of a methyl acrylate-methacrylic acid-methyl methacrylate copolymer were dissolved in a 240 g mixture of methylene chloride and methanol (1:1).

The solution was made into a powder in the same manner as in Example 5.

Example 8

8 g of AS-56C and 16 g of a methyl acrylate-methacrylic acid-methyl methacrylate copolymer were dissolved in a 240 g mixture of methylene chloride and methanol (1:1).

The solution was made into a powder in the same manner as in Example 5.

Example 9

4 g of AS-56C and 16 g of a methacrylic acid-methyl methacrylate copolymer were dissolved in a 240 g mixture of isopropyl alcohol and acetone (6:4).

The solution was made into a powder in the same manner as in Example 5.

Example 10

8 g of AS-56C and 16 g of a methacrylic acid-methyl methacrylate copolymer were dissolved in a 240 g mixture of isopropyl alcohol and acetone (6:4).

The solution was made into a powder in the same manner as in Example 5.

Example 11

4 g of AS-56C, 8 g hydroxypropyl methyl cellulose phthalate, and 8 g of a methyl acrylate-methacrylic acid-methyl acrylate copolymer were dissolved in a 160 g mixture of methylene chloride and methanol (1:1).

The solution was made into a powder in the same manner as in Example 5.

Example 12

8 g of AS-56C, 8 g hydroxypropyl methyl cellulose phthalate, and 8 g of a methyl acrylate-methacrylic acid-methyl acrylate copolymer were dissolved in a 160 g mixture of methylene chloride and methanol (1:1).

The solution was made into a powder in the same manner as in Example 5.

4. Brief Description of the Drawings

Figure 1 illustrates X-ray diffraction of AS-56C crystals.

Figure 2 illustrates X-ray diffraction of a physical mixture of 1 part AS-56C crystals and 4 parts hydroxypropyl methyl cellulose.

Figure 3 illustrates X-ray diffraction of a physical mixture of 1 part AS-56C crystals and 4 parts hydroxypropyl methyl cellulose acetate succinate.

Figure 4 illustrates X-ray diffraction of a physical mixture of 1 part AS-56C crystals and 4 parts methyl acrylate-methacrylic acid-methyl methacrylate copolymer.

Figure 5 illustrates X-ray diffraction of a physical mixture of 1 part AS-56C crystals and 4 parts methacrylic acid-methyl methacrylate copolymer.

Figure 6 illustrates X-ray diffraction of the composition of Example 1.

Figure 7 illustrates X-ray diffraction of the composition of Example 2.

Figure 8 illustrates X-ray diffraction of the composition of Example 3.

Figure 9 illustrates X-ray diffraction of the composition of Example 4.

Figure 10 illustrates X-ray diffraction of the composition of Example 5.

Figure 11 illustrates X-ray diffraction of the composition of Example 6.

Figure 12 illustrates X-ray diffraction of the composition of Example 7.

Figure 13 illustrates X-ray diffraction of the composition of Example 8.

Figure 14 illustrates X-ray diffraction of the composition of Example 9.

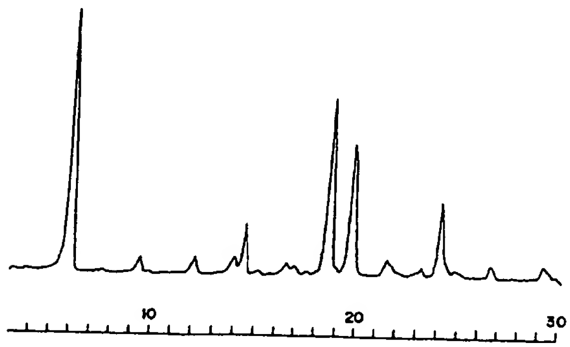
Figure 15 illustrates X-ray diffraction of the composition of Example 10.

Figure 16 illustrates X-ray diffraction of the composition of Example 11.

Figure 17 illustrates X-ray diffraction of the composition of Example 12.

[Translator's note: Japanese text below reads "Figure No. __."]

第 1 図



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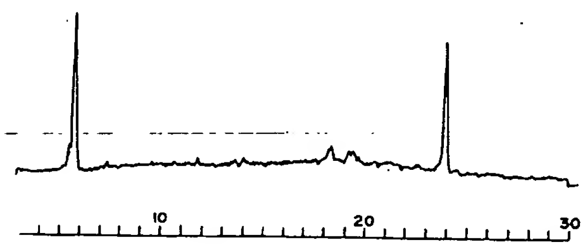

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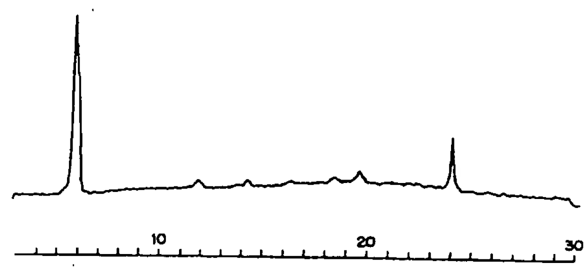

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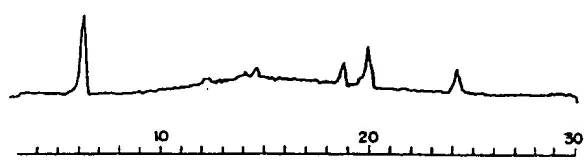

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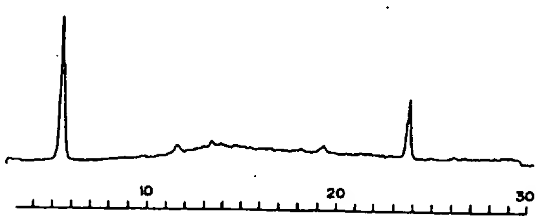

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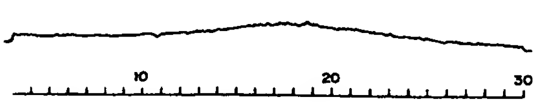

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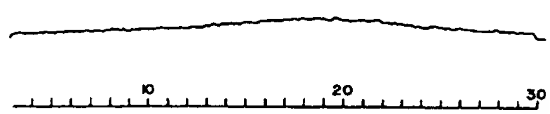
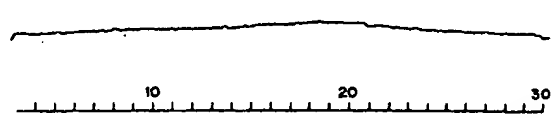
第 8 図



第 9 図

第 10 図



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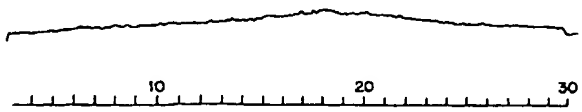

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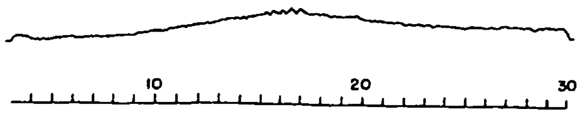
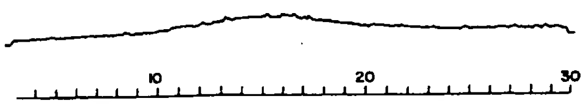


第13図

第14図



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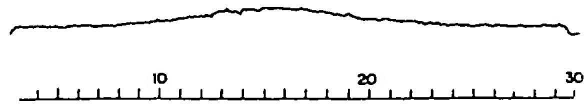

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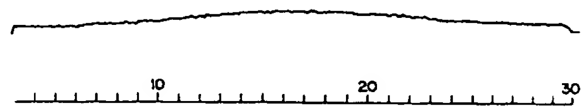

第17図